PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Understanding COVID-19; Are children the key?
AUTHORS	Warner, Suz Richter, Alex Stamataki, Zania Kelly, Deirdre

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Lael M. Yonker Institution and Country: Massachusetts Gen Hosp, United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	03-Mar-2021

GENERAL COMMENTS	Understanding COVID-19; Are children the key? The authors write a very well-written, succinct review of how COVID-19 impacts children as compared to adults. They highlight differences in prevalence (accurately noting likely underestimates), innate immunity, adaptive immunity and cytokine responses. They also discuss viral receptors, transmission, and viral factors/lack of vaccination that may have differences in children. This covers a wide range of important topics related to COVID in children and they nicely touch on key aspects. There are some areas that are stronger than others but overall, this is an easy-to-digest review of the latest knowledge on pediatric impact of COVID-19. Specific comments: - Highlights are compelling yet the lay out of the paper doesn't quite hold this same compelling lay out. Changing the section headings to carry this storyline will help, rather than just itemizing the topics the authors cover. - The table is a bit hard to take in, and I imagine there must be some data out there on the missing "n/a" boxes. References for each finding should be embedded within each appropriate box. Alternatively, the authors could consider a heatmap to color code changes as a way of making it less busy/easier to interpret. Typo- NK cells are in monocyte cell for Asymptomatic children. - It is important throughout to make clarify when the authors are referring to acute COVID in adults vs children, and PIMS-TS. - Innate immunity: worth including the role of Type I IFN deficiency/autoantibodies as a risk for developing severe acute COVID. (https://pubmed.ncbi.nlm.nih.gov/32972996/) - Adaptive immunity: Recently published manuscript highlighting differences in adaptive immune responses between kids and adults, mild and severe: https://pubmed.ncbi.nlm.nih.gov/33589825/ - Cytokine storm: again, the authors should define which disease type they are referring to (adult COVID, pedi COVID, PIMS)

	- "Based on our experience" should be removed (last paragraph in cytokine storm section)- there is ample published evidence to support this is a post-infectious inflammatory illness. https://pubmed.ncbi.nlm.nih.gov/32598831/ https://pubmed.ncbi.nlm.nih.gov/33625505/ - The immunity section is comprehensive but then the remaining sections are a bit disjointed. The authors are currently missing the opportunity to tie these sections back into the goals outlined in the highlights. - ACE2: ACE2 expression in the upper airways is lower in younger children: https://pubmed.ncbi.nlm.nih.gov/32827525/ ACE2 expression in the lower airways may explain why children don't get lower airway infection with acute infection although it has not been shown. - Transmission: Referencing a news source rather than a peer reviewed publication weakens this section and should be removed. A recent review on aerosol transmission that may be helpful: https://pubmed.ncbi.nlm.nih.gov/33624927/ - Vaccine section is a great section but more of a news report than a review. The referenced news link should be switched to a peer reviewed publication. Excellent section to address concerns around vaccination's sustained effect, rational for vaccinating children who will be reservoirs for the virus. Highlighting age-specific guidelines of today will be quickly outdated as vaccine guidelines are rapidly changing.

REVIEWER	Reviewer name: Dr. S K Kabra Institution and Country: AIIMS, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India. Competing interests: None
REVIEW RETURNED	28-Feb-2021

GENERAL COMMENTS	In this narrative review authors discus various aspects of iatrogenesis of Covid 19 infection in children and adults. They tried to discuss most of the available information on the subject and conclude that COVID-19 pandemic has highlighted gaps in our knowledge of viral immunology between adults and children. Deciphering the mechanism of children's resistance to disease could help target therapeutic interventions in adults and should be of high priority for future investigations 1. In the introduction add few lines about how authors did search? 2. In beginning a paragraph may include: likely pathogenesis like other similar viral infection: interaction with dendritic cells, phagocytes, T cell, B cell interaction etc 3.A paragraph about available information on immune response for covid 19 and obvious differences between children and adults. 4. Discuss each immune step and compare between children and adults. Try to provide explanation for difference and its implication on clinical manifestations and role in preventive aspect. Abstract: It is desirable to provide important evidence in abstract that has implication on clinical manifestations etc Key statements: These are unclear. First statement " significant differences--" is based on information available in the review while second and third statements are more of recommendations and not supported from the contents of review. Statement like children are reservoir of infection is not based on any evidence Minor comments Reason for citing RVS/Mycoplasma is unclear as both has different manifestation (age etc) Though authors mention mild illness in children, severe illness in

	children and MISC and tried to compare with severe illness in adults. They tried to suggest that cytokine storm is similar in children with MISC and ARDS in adults. However tehse two conditions are difefrent (ARDS occur in continuity of infection as indicated by RTPCR positive while MISC is without acute infection in majority) Therefore sugegst to compare immune steps in mild/ severe illness and may mention diferences. Separately may discuss MISC and cytokine storm with some explanantions.

VERSION 1 – AUTHOR RESPONSE

Dear Dr. Escobedo,

Thank you for considering our manuscript titled "Understanding COVID-19; Are children the key?" for publication in BMJ Paediatrics Open.
We thank the reviewers for their helpful comments and suggestions, and have modified the manuscript accordingly. We have addressed the reviewers' comments below and have provided the corresponding 'Lines' in the manuscript for ease of reference. We have also highlighted the changes in the 'Main Document - marked copy' as advised.

We look forward to hearing from you.
Kind Regards,
Suz Warner

Point by point responses to Reviewer 1's comments
1. In the introduction add a few lines about how authors did the search?

Response: A description of the literature search has been added to the 'Introduction' section. Lines 188-192

2. Include a paragraph of the likely pathogenesis and immune cell interaction of viral infections.

Response: A paragraph has been created to describe the host's innate and adaptive responses to viral infections. Lines 224-241

3. Provide a paragraph on the available information on the immune responses to COVID-19 and the differences between children and adults.

Response: In our initial manuscript, we did set out the differences in the innate and adaptive immune responses and the cytokine production to COVID-19 between children and adults. Lines 223-411 and Figures 1,2 & 3 and Tables 1 & 2.

4. Discuss each immune step and compare between children and adults. Try to provide explanation for difference and its implication on clinical manifestations and role in preventive aspect.

Response: We have altered the relevant sections of 'CHILDHOOD AND ADULT IMMUNE RESPONSES TO SARS-CoV-2' to incorporate the Reviewer's suggestion of linking immune differences with the clinical implications.
Lines 223-411 and Figures 1,2 & 3 and Tables 1 & 2.

5. Provide evidence in abstract of clinical manifestations.

Response: Description of the clinical features/syndromes encountered by children and adults have been included in the abstract.
Lines 118-119 and Lines 123-126

6. Key statements.

Response: Rewording of Key Statements 2 and 3 have been made to reflect emerging information and recommendations. Lines 137-138

7. Reason for citing RVS/Mycoplasma is unclear as both have different manifestation (age etc).

Response: RSV and Mycoplasma infections were mentioned in the original manuscript to emphasis the difference in clinical disease these common viral infections have on children compared to COVID-19. Children with RSV/Mycoplasma manifest more respiratory symptoms, and a larger percentage will deteriorate compared to the milder phenotype of paediatric COVID-19.
We have now removed this excerpt. Lines 166-167

8. Discuss the similarities and differences in the cytokine storm seen in adult COVID-19 and PIMS-TS/MIS-C.

Response: The immune aspects and clinical features are described in severe adult COVID-19 and PIMS-TS/MIS-C in the Cytokine storm section.
We have clarified that these syndromes are different but have highlighted the striking parallels in their immune signature and the biomarker levels observed. Lines 372-411 and Tables 1 &2.

Point by point responses to Reviewer 2's comments
1. Change the section headings to carry the storyline.

Response: Section headings have been rearranged. The 'Transmission' section has been brought forward and the 'Humoral' and the 'Anamnestic' has been swapped around to aid with the flow of the manuscript. Lines 196-220 and LINES 321-370

2. It is difficult to interpret the original Table and references should be embedded within each appropriate box.

Response: We agree that the table was hard to interpret.
The information in the table has been broken down into 3 separate figures and two tables. References are included at the end of each Figure/Table. Figures 1,2 & 3 and Tables 1 & 2.

3. Typo – NK cells

Response: Natural Killer cells are from the lymphocyte cell line and we have elected to keep this but have elaborated that they are part of our innate immunity. Lines 271-273

4. There needs to be more clarification of clinical syndromes assoc. with SARS-CoV2 infection

Response: This is a very important point and a sentence has been inserted clarifying the different clinical syndromes; adult COVID-19, paediatric COVID-19 and PIMS-TS. Lines 191-192

5. Suggestion to include the role of IFN Type 1 deficiency/autoantibodies (https://pubmed.ncbi.nlm.nih.gov/32972996/

Response: The crucial anti-viral role of IFN is stated in relation to antigen presenting cells. IFN immune escape is mentioned. We have also incorporated the significance of autoantibodies directed against IFN and the detrimental effect select immune deficiencies may have with thanks. Lines 293-296

6. Suggestion to include findings of the recent manuscript on humoral immunity in SARS-CoV2 infection https://pubmed.ncbi.nlm.nih.gov/33589825/

Response: We have incorporated the description of innate cell activation via surface Fc receptors.
Lines 229-230 and Lines 328-329 and Lines 336-338

7. Clarify the different clinical syndromes associated with the cytokine storm.

Response: We have specified the different hyperinflammatory syndromes seen in adult COVID and PIMS-TS/MIC-S. Lines 373-377 and Lines 385-391

8. Based on our experience' should be removed.

Response: This part of the sentence has been omitted. Line 407

9. ACE2 expression in childhood

Response: We have emphasised the near Normal distribution of ACE expression with age. Lines 414-416

10. Transmission reference source

Response: The original peer reviewed publication has been kept and referenced for this section. Lines 196-199

11. Vaccine section

Response: Peer reviewed publications are included. Lines 434-437

Editor in Chief Comments to Author

Original table is complex. It may be better as two tables or presenting some of the data as a figure. Figures would help the review.

Response: Many thanks for your time and consideration of our manuscript.
We agree that the original table is complex and difficult for the reader to decipher. We have taken on your advice to split the table into a combination of Figures and Tables. Figures 1,2 & 3 and Tables 1 & 2.